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An Efficient Synthesis of 1,5-Benzodiazepines Using $AlCl_3$ Under Solvent Free Condition

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A mild, efficient and rapid method for synthesis of 1,5-benzodiazepines from *o*-phenylenediamine and different ketones has been developed by using aluminium chloride as a catalyst. The higher yield and purity of products is additional feature of the methodology.

Key Words: 1,5-Benzodiazepines, *o*-Phenylenediamine, Aluminium chloride, Ketones, Solvents.

INTRODUCTION

Benzodiazepines have wide spectrum of biological activity. In the past decades they are widely used as anticonvulsant, analgesic, hypnotic, sedative and antidepressive agents[1]. In addition 1,5-benzodiazepines have found applications as valuable intermediate in synthesis of derivatives such as triazolo- and oxadiazolo-benzodiazepines. Some benzodiazepine derivatives are also used in industry, such as light sensitive material and also as antiinflammatory agents[2].

Because of their wide range of pharmacological activity and industrial synthetic applications, many methods for their preparation are reported in the literature. These includes condensation reactions of *o*-phenylenediamine with α,β-unsaturated carbonyl compounds[3], β-haloketones[4] or ketones in the presence of BF_3- etherate[5], $NaBH_4$[6] polyphosphoric acid[7], MgO and $POCl_3$[8], ytterbium perfluorooctanesulfonate[2] superacid sulfated zirconia[9] and $Ln(OTf)_3$[10]. Stoichiometric amount of ionic liquid-promoted[11] and microwave irradiated[12] preparation of 1,5-benzodiazepines have also been reported. In spite of some good procedures available to chemists, many of these suffer from disadvantages like requirement of anhydrous conditions, use of strong acid or organic solvents, elevated temperature, prolonged reaction time *etc*. Some of these catalysts break up into even more hazardous and non degradable toxic compounds during work-up. Therefore, search for a safe and mild protocol for synthesis of these important molecules is important. Here we wish to report use of aluminium chloride as a catalyst for an efficient synthesis of 1,5-benzodiazepines under solvent-free conditions.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Ketones were distilled prior to use, *o*-phenylenediamine was recrystallized from hot water containing sodium hydrosulfide and treated with decolorizing charcoal. IR spectra were recorded in KBr discs on a Perkin-Elmer 240C analyzer. ^{1}H NMR spectra were recorded on Varian Gemini 300 (300 MHz) spectrometer using TMS as internal standard.

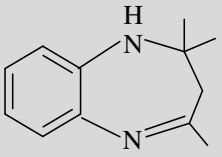
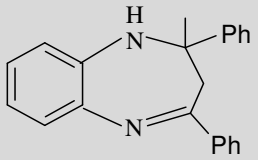
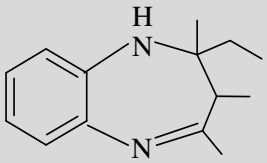
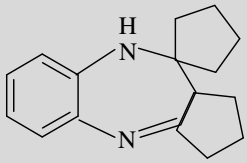
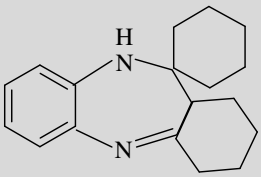
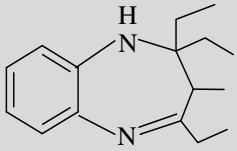
General procedure for preparation of 1,5-benzodiazepines: To a stirred mixture of *o*-phenylenediamine (5 mmol) and ketone (10 mmol) at room temperature was added $AlCl_3$ (10 mmol). Further the reaction mixture was stirred for time given in Table-1. After completion of reaction (monitored by TLC), the reaction mass was diluted with ethyl acetate (20 mL), washed with saturated $NaHCO_3$ solution (3 × 15 mL) and then with brine (3 × 10 mL). The organic layer was dried over anhydrous sodium sulphate. Evaporation of the solvent gave the crude product which was purified by recrystallization from ethyl acetate: hexane mixture.

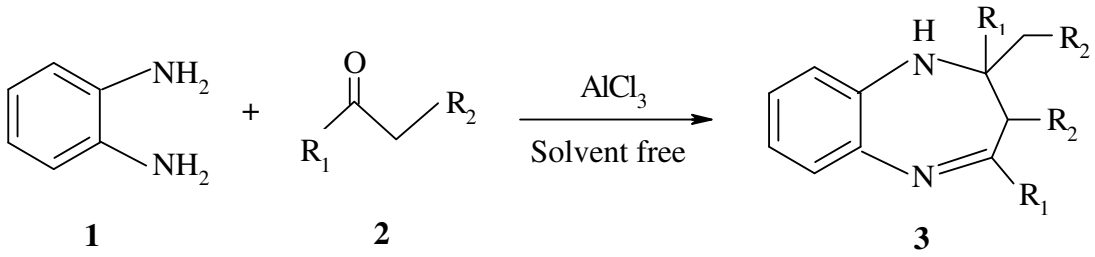
Spectral analysis

2,2,4-Trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3a): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 6H), 2.22 (s, 2H), 2.38 (s, 3H), 3.04 (br. 1H), 6.75-7.16 (m, 4H); IR (KBr, ν_{max}, cm^{-1}): 3292, 1644 and 1594.

2, 4-Diphenyl-2-methyl-2, 3-dihydro-1*H*-1,5-benzodiazepine (3b): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72 (s, 3H), 2.94 (d, 1H), 3.13 (d, 1H), 3.51 (br. 1H), 6.86-7.58 (m, 14H); IR (KBr, ν_{max}, cm^{-1}): 3240, 1630 and 1584.

TABLE-1
REACTIONS BETWEEN *o*-PHENYLENEDIAMINE AND KETONES IN PRESENCE OF $AlCl_3$

Reactant	Product	Time (min)	Yield (%)	m.p. (ºC) [Lit.][2]
Acetone	 **3a**	30	96	125 [126]
Acetophenone	 **3b**	40	94	150-151 [151-152]
2-Butanone	 **3c**	40	92	138-139 [137-138]
Cyclopentanone	 **3d**	50	96	133-134 [134-135]
Cyclohexanone	 **3e**	40	90	137-138 [137-139]
3-Pentanone	 **3f**	55	95	143-144 [144-145]



1 **2** **3**

Scheme-I: Synthesis of 1,5-benzodiazepines

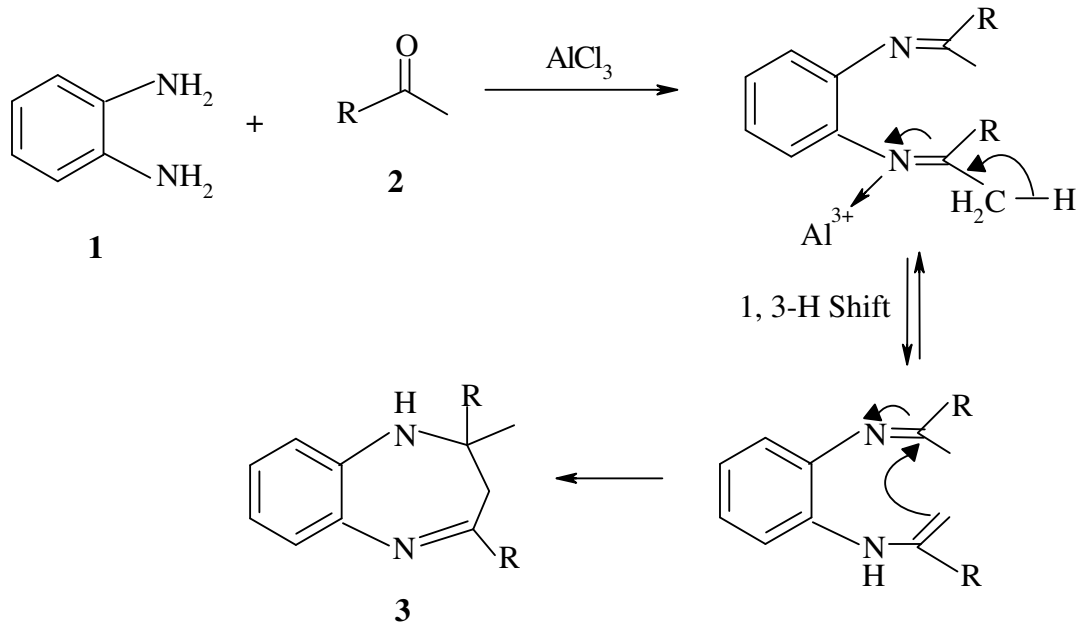
2,3,4-Trimethyl-2-ethyl-2, 3-dihydro-1*H*-1, 5-benzodiazepine (3c): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, 3H), 1.21 (t, 3H), 1.67 (q, 2H), 2.12 (m, 2H), 2.30 (s, 3H), 2.66 (q, 2H), 3.35 (br. 1H), 6.80-7.35 (m, 4H); IR (KBr, ν_{max}, cm^{-1}): 3338, 1640 and 1590.

10-Spirocyclopentan-1,2,3,9,10,10a-hexahydrobenzo-[b]-cyclopenta[e][1,4]diaze-pine (3d): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02-2.26 (m, 13H), 3.22 (m, 2H), 3.70 (br. 1H), 6.70-7.25 (m, 4H); IR (KBr, ν_{max}, cm^{-1}): 3334, 1656 and 1600.

10-Spirocyclohexan-2,3,4,10,11,11a-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine (3e): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98-2.38 (m, 17H), 3.20 (m, 2H), 3.72 (br. 1H), 6.52-7.20 (m, 4H); IR (KBr, ν_{max}, cm^{-1}): 3300, 1640 and 1600.

RESULTS AND DISCUSSION

Herein, the use of aluminium chloride as a catalyst for an efficient synthesis of 1,5-benzodiazepines by condensation of *o*-phenylenediamine with ketones under solvent free conditions



Scheme-II: Mechanism of the formation of benzodiazepines

is reported. The removal of excess aluminium chloride is also simple process and yields obtained are also good as compared with literature yields.

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